Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Rapamune® Solution

Oral solution

Each 1 mL contains: sirolimus 1 mg

Inactive ingredients and allergens: See section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Further information'.

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Rapamune® is intended to suppress the immune system. This medicine is intended for prevention of transplant rejection in patients receiving a kidney transplant.

Therapeutic group: selective immunosuppressant.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine (see section 6).
- you are allergic to peanuts or soya.

Special warnings regarding use of the medicine

Before treatment with Rapamune®, tell your doctor if:

- you are pregnant, see the section 'Pregnancy, breastfeeding, and fertility'.
- you have impaired liver function or have had a disease which may have affected your liver. Your dose may need to change and you may need additional blood tests.
- you have problems with your immune system. Rapamune®, like other immunosuppressive medicines, may decrease your body's immune resistance, and may increase your risk of developing cancer of the lymphoid tissues and skin.
- you have a body mass index (BMI) greater than 30 (weight[kg]/height^2 [m^2]). You may be at increased risk of abnormal wound knitting and scabbing.
- you are at high risk for transplant rejection (such as if you had a previous transplant that was lost to rejection).

Rapamune® and exposure to light and sun

Exposure to sunlight and UV light can increase your risk of developing skin cancer; therefore, avoid exposure to the sun and be sure to have proper protection (long

clothing, hat, high SPF sunscreen, etc.).

Children and adolescents
There is no information regarding the safety and effectiveness of using this medicine in children and adolescents less than 18 years old.

Tests and follow-up
During your course of treatment, you will be referred for blood tests to monitor the levels of this medicine in your blood, and for periodic tests to monitor your kidney function and your blood fat (cholesterol and/or triglycerides) levels. Your doctor may also order a test for liver function.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
- other immunosuppressant medicines
- medicines for reducing high blood pressure or medicines for heart problems such as nicardipine, verapamil, diltiazem.
- medicines used to treat ulcers or other digestive system problems such as cisapride, cimetidine, metoclopramide.
- antibiotics or antifungal medicines such as clotrimazole, fluconazole, itraconazole, clarithromycin, erythromycin, telithromycin, troleandomycin, rifabutin. It is not recommended that Rapamune® be taken with rifampicin, ketoconazole, voriconazole.
- anti-epileptic medicines such as carbamazepine, phenobarbital, phenytoin.
- danazol (used in the treatment of gynaecological disorders).
- bromocriptine (used in the treatment of Parkinson's disease and various hormonal disorders).
- protease inhibitors used to treat HIV and hepatitis C such as ritonavir, indinavir, boceprevir, and telaprevir.
- products containing St. John's Wort (*Hypericum perforatum*).
- letermovir (an antiviral medicine to prevent the disease caused by cytomegalovirus (CMV)).
- If you are planning to get vaccinated, tell your doctor or pharmacist that you are receiving Rapamune®. The use of live vaccines should be avoided during treatment with this medicine.
- medicines used to reduce cholesterol and triglycerides in your blood such as statins and fibrates:
  The use of Rapamune® may lead to increased levels of cholesterol and triglycerides (fats) in your blood. This increase may require treatment. Statin and fibrate medicines used to treat elevated levels of cholesterol and triglycerides, have been associated with an increased risk of muscle breakdown (rhabdomyolysis). Tell your doctor if you are taking such medicines.
- ACE inhibitors, a type of medicine for reducing blood pressure. The combined use of ACE inhibitors with Rapamune® may cause allergic reactions. Tell your doctor if you are taking such a medicine.

Using this medicine and food
If you take this medicine after food, then you should make sure to always take it after food. If you take this medicine without food, then you should make sure to always

take it without food.
It is important to follow this direction because food can affect the level of medicine in your bloodstream, so taking your medicine in a consistent way (either with or without food) helps blood levels of this medicine remain more stable.
Do not take this medicine with grapefruit juice.

Pregnancy, breastfeeding, and fertility
Pregnancy
Do not use the medicine during pregnancy unless your doctor has decided the treatment is clearly necessary.
Women of childbearing age must use an effective method of contraception during treatment and for 12 weeks after treatment with Rapamune® has stopped.
If you are pregnant or breastfeeding, think you are pregnant or are planning to become pregnant, consult your doctor before taking this medicine.
Breastfeeding
It is not known whether Rapamune® passes into breast milk. Women taking Rapamune® should discontinue breastfeeding.
Fertility
Decreased sperm count has been associated with the use of Rapamune® and usually returns to normal once treatment is stopped.

Driving and using machines
Rapamune® use is not expected to affect your ability to drive. If you are uncertain, consult your doctor.

Important information about some of this medicine's ingredients
Rapamune® Solution contains soya oil. Do not use this medicine if you are allergic to peanuts or soya – see the section 'Before using this medicine'.
Rapamune® Solution contains up to 3.17% vol ethanol (alcohol). An initial dose of 6 mg of this medicine contains up to 150 mg of alcohol which is equivalent to 3.8 mL beer or 1.58 mL wine. This alcohol may be harmful for those suffering from alcoholism, epilepsy and liver disease, as well as for pregnant women, breastfeeding women, and children. Alcohol may increase or modify the effect of other medicines. One 4 mg dose of this medicine or less contains a very small amount of ethanol (100 mg or less) which is considered too low to be harmful.

3. HOW TO USE THIS MEDICINE?
Always use this medicine according to your doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by your doctor only.
Your first dose will be given immediately after the transplant operation.
During your course of treatment, your doctor will order blood tests to measure Rapamune® concentrations in your blood, and will adjust your dosage depending on the results.

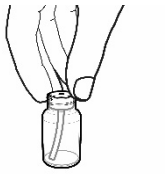
Do not exceed the recommended dose.

If you are taking ciclosporin in addition to Rapamune®, then you must take the two

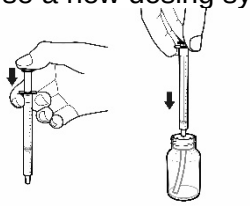
medicines approximately 4 hours apart.
Rapamune® Solution is for oral use only. Consult your doctor if you have difficulty taking the oral solution.
Take this medicine consistently, either with or without food. See additional information in the section 'Using this medicine and food'.
Rapamune® Solution is a liquid medicine, so you must use the special syringe to measure the correct amount of medicine. For your convenience, you will find enclosed a dosing syringe, snap-on safety cap, and carrying case for measuring your dose and carrying it.
Be careful to measure your dose exactly using the enclosed syringe.
The dosing syringe and safety cap are to be used once! Do not rinse them. Discard them after use!
See detailed instructions in the following instructions for use:

Using this medicine:

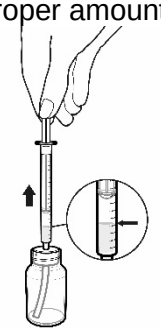
1. Open the bottle of solution. To open the safety cap, squeeze the smooth areas on both sides of the cap and twist counter clockwise.
   When using for the first time, attach the adapter (a plastic tube with a cap) to the bottle by inserting the adapter until its top edge is flush with the lip of the bottle. Do not remove the adapter from the bottle once inserted.



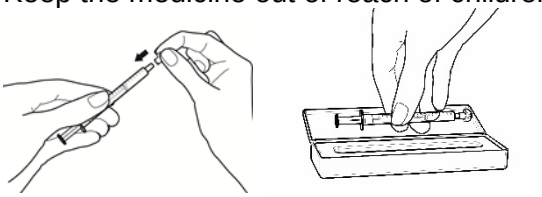
2. With the plunger fully depressed, insert one of the dosing syringes into the opening in the adapter.
   Use a new dosing syringe each time (the dosing syringe is yellowish-brown).



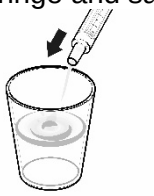
3. Withdraw the proper amount of Rapamune® solution by gently pulling up (out) the plunger of the dosing syringe until the amount of solution matches the mark for the proper amount on the dosing syringe.
   Keep the bottle in an upright position when withdrawing the solution into the dosing syringe.
   If bubbles form in the solution in the dosing syringe while you are withdrawing the dose, empty the syringe into the bottle and repeat the withdrawal procedure. You may need to repeat step 3 more than once to withdraw the proper amount.



4. You may need to carry your medication with you.
If you need to take the filled dosing syringe with you:
After withdrawing the proper amount into the dosing syringe, place the safety cap on the syringe – the cap will snap onto the syringe.
Place the dosing syringe with safety cap in the carrying case provided in the pack.
You may keep the dosing syringe filled with solution at room temperature (up to 25°C) or in the refrigerator and use it within 24 hours.
Keep the medicine out of reach of children.



5. Empty the dosing syringe into only a glass or plastic cup holding at least **60 mL (1/4 cup) of water or orange juice**. Stir well for one minute and drink immediately. Refill the glass with at least 120 mL (1/2 cup) of water or orange juice, stir well, and drink immediately. Do not use grapefruit juice or any other liquid for dilution.
Use only a glass or plastic cup to dilute Rapamune® solution. The dosing syringe and safety cap are to be used once and discarded after use.



When stored in a refrigerator a haze may develop in the solution in the bottle. This haze does not affect the medicine's efficacy. If this happens, take the Rapamune® solution out of the refrigerator for a short while to allow it to reach room temperature and shake gently until the haze disappears.

If you have accidentally taken a higher dosage
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
If you forget to take this medicine at the scheduled time, take it as soon as you remember, but make sure to have at least 4 hours between taking Rapamune® and the next dose of ciclosporin. After that, continue to take your medicines as usual, taking your next dose at the usual time, and consult your doctor. Do not take a double dose to make up for a forgotten dose,
Remember to always take Rapamune® and ciclosporin 4 hours apart.
If you miss a dose of this medicine completely, you should inform your doctor.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine

Do not stop taking this medicine unless your doctor tells you to, as you risk losing your transplant.

Do not take medicines in the dark! Check the label and dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Rapamune® may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Allergic reactions

Contact your doctor immediately if you notice the following symptoms, which may be signs of a serious allergic reaction:

swollen face, tongue and/or back of the mouth (pharynx) and/or difficulties in breathing (angioedema), or a skin condition in which the skin can peel off (exfoliative dermatitis).

Kidney damage with low platelet count and low red blood cell count with or without rash

Contact your doctor immediately if you experience symptoms such as bruising or rash, changes in your urine, or changes in behaviour, or any other effect that is serious/unusual/prolonged. This is because Rapamune® can increase the risk of kidney damage associated with low platelet count and low red blood cell count with or without rash (thrombocytopaenic purpura/haemolytic uraemic syndrome).

Tendency to get infections

Rapamune® suppresses your body's immune system to prevent transplant rejection. As a result, your immune resistance is reduced and you may therefore be more sensitive to infections such as skin, mouth, stomach and digestive system, lungs, and urinary tract infections. **Contact your doctor if** you experience serious, unusual, or prolonged symptoms.

Additional side effects

Very common side effects (affect more than 1 in 10 people):

- fluid collection around the kidney
- swelling of the body including hands and feet
- pain
- fever
- headache
- increased blood pressure
- stomach pain, diarrhoea, constipation, nausea
- low red blood cells, low blood platelets
- increased fat in the blood (cholesterol and/or triglycerides), increased blood sugar, low blood potassium, low blood phosphorus, increased LDH (lactate dehydrogenase) in the blood, increased creatinine in the blood
- joint pain
- acne

- urinary tract infection
- pneumonia and other bacterial, viral, and fungal infections
- a reduced number of infection-fighting cells in the blood (white blood cells)
- diabetes
- abnormal results of liver function tests, elevated liver enzymes such as AST and/or ALT
- rash
- protein in the urine
- menstrual disorders (including absent, infrequent or heavy periods)
- slow healing of wounds (this may include separation of the layers of a surgical wound or stitch line)
- rapid heart rate
- a general tendency for fluid to collect in various tissues.

Common side effects (affect up to 1 in 10 people):
- infections (including life-threatening infections)
- blood clots in the legs
- blood clots in the lungs
- mouth sores
- fluid collection in the abdomen (ascites)
- kidney damage with low blood platelet count and low red blood cell count, with or without rash (haemolytic uraemic syndrome)
- low neutrophil count (of a type of white blood cells)
- deterioration of bone (osteonecrosis)
- inflammation that may lead to lung damage, fluid around the lungs
- nose bleeds
- skin cancer
- kidney infection
- ovarian cysts
- fluid collection in the sac around the heart (that in some cases may decrease the heart's ability to pump blood)
- inflammation of the pancreas
- allergic reactions
- shingles
- cytomegalovirus infection (CMV)

Uncommon side effects (affect up to 1 in 100 people):
- cancer of the lymph tissue (lymphoma/post-transplant lympho-proliferative disorder), combined low count of red blood cells, white blood cells, and platelets
- bleeding from the lung
- protein in the urine, occasionally severe and associated with side effects, such as swelling (nephrotic syndrome)
- scarring in the kidney that may reduce kidney function
- too much fluid collecting in the tissues due to irregular lymph function
- low blood platelets, with or without rash (thrombocytopaenic purpura)
- serious allergic reactions that can cause peeling of the skin
- tuberculosis
- Epstein-Barr virus (EBV) infection
- infectious diarrhoea with *Clostridium difficile*
- serious liver damage

Rare side effects (affect up to 1 in 1,000 people):
- protein build-up in the air sacs of the lungs that may interfere with breathing
- serious allergic reactions that can affect blood vessels (see above paragraph on allergic reactions)

Side effects of unknown frequency (the frequency of these effects has not yet been established):
- posterior reversible encephalopathy syndrome (PRES), a serious nervous system syndrome that has the following symptoms: headache, nausea, vomiting, confusion, seizures, and visual loss. Should any of these symptoms occur together, contact your doctor.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Prevent poisoning! This and any other medicine should be kept in a closed place, out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C).
- Keep the bottle in its original package in order to protect from light.
- Once the bottle has been opened, keep it refrigerated and use its content within 30 days of first opening. If necessary, you may store the bottle at room temperature, up to 25°C, for a short period of time, but no longer than 24 hours.
- Once the dosing syringe has been filled with the proper amount, the medicine can be kept in the syringe for 24 hours at room temperature, up to 25°C, or in a refrigerator (2°C-8°C).
- Once the contents of the dosing syringe have been diluted in water or orange juice (according to the instructions in this leaflet), the preparation should be drunk immediately.

6. FURTHER INFORMATION

In addition to the active ingredient, this medicine also contains:
polysorbate 80; phosal 50 PG (phosphatidylcholine, soya-fatty acids, ethanol, monodiglycerides, propylene glycol, ascorbyl palmitate).

Each 1 mL of solution contains:
- up to 25 mg ethanol
- 20 mg soya oil
- about 350 mg propylene glycol (E1520)

What the medicine looks like and contents of the pack:

Rapamune® solution is pale yellow to yellow.
It is supplied in a carton containing:
- 1 bottle (yellowish-brown glass) containing 60 mL of Rapamune® solution
- 1 bottle adapter
- 30 single-use dosing syringes (dark plastic)
- syringe carrying case.

Registration holder's name and address: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725

Registration number of the medicine in the Ministry of Health's National Drug Registry: 122-12-30229

Revised in 10/2021 according to MOH guidelines.